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Case Study

Total pancreatectomy with islet autotransplantation – a new pain management strategy in chronic pancreatitis?

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Key Learning Points

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Total pancreatectomy and islet autotransplantation (TPIAT) is a procedure that is considered as a last resort for patients with chronic pancreatitis whose quality of life is significantly interfered with by chronic severe intractable pain. It is considered following a stepwise approach to pain control which includes pharmacological, endoscopic and surgical measures. Usually, however, pressures on healthcare systems are such that these patients do not receive appropriate specialist care and end up being marginalised in society, unable to integrate or contribute to it either. TPIAT achieves significant pain reduction in 80-90% of patients who undergo the procedure with 20-30% being pain-free. The islet autotransplantation is done to ameliorate type 3c diabetes that results after total pancreatectomy and some patients remain euglycemic. It should be noted however that all patients eventually become diabetic within the first 5 years post-surgery, although the diabetes that results is much easier to control than that with type 3c. There also is emerging evidence that this translates to better long-term survival compared to total pancreatectomy alone.

Getting the timing of when TPIAT happens in the natural history of a patient with chronic pancreatitis is also vital. This should ideally be before opioid-induced hyperalgesia occurs and the pain itself becomes independent of actual peripheral nociceptive input of the pancreas. Get this wrong and the patient's pain does not improve. Additionally, it is important to proceed before the chronic inflammation results in islet damage and below threshold islet yield for autotransplant. Patient XY likely had the procedure in time. She currently is entirely pain-free, back at work and functional with excellent islet function more than a year after TPIAT.

Introduction

Chronic pancreatitis (CP) is a long-standing inflammatory disease of the pancreas, which affects ~0.024% of the UK's population with 6.7/100,000 new cases diagnosed every year[1]. Although long-term alcohol use and gallstones remain the main cause of CP amongst adults, another large group of CP patients (10-30%) are those with no identifiable cause of the disease, the so-called idiopathic CP1. Other rarer causes include biliary disease, pancreatic duct obstruction, hyperlipidaemia, hypercalcaemia, as well as autoimmune and hereditary pancreatitis[2].

Chronic inflammation, fibrosis and loss of acinar, ductal & islet cells are the key histopathological hallmarks of CP[3]. Consequently, more than 50% of patients develop exocrine insufficiency, characterised by fat malabsorption, steatorrhea, deficiency of the fat-soluble vitamins A, D, E & K, malnutrition and weight loss[4]. In more than half of the patients, the loss of islets can also result in a specific type of diabetes, known as "brittle" type 3c diabetes mellitus[4]. This pancreatogenic form of diabetes differs from type 1 and type 2 diabetes in not only that the function of insulin is compromised, but also that of glucagon and pancreatic polypeptide.

Pain, however, is by far the most debilitating clinical feature of CP with recent studies showing that the severity of pain is the most significant correlate of the self-reported reduction in quality of life[5]. Pain affects up to 90% of CP patients and it is the main reason for hospital admissions in 93% of cases[6]. It is usually found in the epigastric region, often radiating to the back. The pain severity and pattern can, however, vary substantially amongst patients - some experience only intermittent attacks, while in others the pain is dull & continuous; there is also a subgroup of patients in whom the intermittent attacks occur on top of the constant pain[6]. Unlike in acute pancreatitis, the structural and functional changes observed in CP are irreversible. Consequently, there are no curative options available to patients with CP and current treatments focus on better pain management, improving food absorption and controlling diabetes. Although the

latter two can be managed effectively with pancreatic enzyme and insulin replacement therapy, the intractable pain of CP remains difficult to manage, largely due to our incomplete understanding of its complex pathophysiology. Consequently, many patients eventually have to rely on long-term analgesia, which with time may become ineffective. This report analyses the case of patient XY, a 41-year-old white female with a long-standing history of idiopathic CP, who underwent total pancreatectomy with islet autotransplantation (TPIAT) as a last resort attempt at reducing the severe pain and the dose of opioid medication required to manage it.

History of presenting complaint

XY first presented with acute pancreatitis in 1999, two weeks postpartum. Since the first attack, the patient suffered 8-10 attacks in total, 5 of which resulting in hospital admissions. The patient described the pain as very intense, epigastric, but often radiating to the back, with each attack lasting from 7 to 10 days. The patient had two more children (in 2001 and 2004) and the pancreatic pain became more intense with each pregnancy. Consistently with the classic CP symptoms, XY suffered from steatorrhea, Vit D deficiency, but she never developed diabetes mellitus.

In 2006 she underwent a cholecystectomy, as microlithiasis was suspected to be the cause of her recurrent pancreatitis. The surgery, however, didn't result in any symptomatic relief or cessation of further episodes of pancreatitis. In 2008 a series of genetic tests revealed that the patient does not carry any hereditary pancreatitis genes and she received a diagnosis of idiopathic CP. In 2010 she underwent a bilateral thoracoscopic splanchnicectomy for neurolysis, which resulted in 7 years of being pain-free and not having to take any regular opioid analgesia. In 2017, however, her pancreatitis symptoms returned and since then she's been back on daily opioid analgesia to alleviate the dull background pancreatic pain.

Ongoing medical conditions

- Fibromyalgia
- Gastroesophageal reflux disease
- Iron-deficiency anaemia
- Osteoarthritis
- Restless legs syndrome

Drug history

On admission XY was on the following list of medications:

•	Amitriptyline	40mg	once a day, at night
•	Duloxetine	30mg	twice a day
•	Esomeprazole	20mg	once a day
•	Ferrous fumarate	210mg	twice a day
•	Naproxen	500mg	twice a day
•	Oramorph	40mg	when required
•	Pramipexole	264µg	once a day, at night
•	Zomorph	90mg	twice a day
•	Creon 40000	2 capsules	three times a day, with meals

No known allergies.

Since seeing the pain team as part of the workup for her surgery, XY began to trial reductions in the dose of her daily opioid medications.

Family and social history

XY's father has type 1 diabetes mellitus. Despite her 3 chronic pain conditions, XY still tries to function normally and leads an active lifestyle. She lives with her 3 children and a partner. She works in a pharmacy for 32h/week, walks 1-2 miles to work and occasionally attends the gym. She avoids drinking alcohol, as it exacerbates the symptoms of her CP. She has smoked half to one pack of cigarettes a day for the past 28 years. Before the surgery, she tried to reduce her smoking to 5 cigarettes a day.

Surgery

In the summer of 2019 XY was referred to the hospital to undergo a multidisciplinary assessment programme for TPIAT. The indication for the surgery was to reduce the burden of her chronic pain due to her long-standing history of CP. The first stages of the evaluation were carried out by the surgical and the diabetology teams, coordinated by a specialist nurse. Her CT scan revealed a bulky calcified pancreatic head and biliary dilation of an uncertain cause down to the level of the ampulla. The pancreatic duct, however, was not dilated. Her meal tolerance test showed a normal glucose & insulin response, suggesting the endocrine function of her pancreas was not compromised. Following further assessments by the pain specialist, psychology, anaesthesia and gastroenterology teams, XY was recommended by all teams as suitable to undergo the procedure.

The patient was made aware of the fact that the surgery might not improve her hitherto symptoms and that islet autotransplantation is unlikely to completely remove the need for insulin treatment post-surgery. Nonetheless, the patient was keen to undergo the surgery in an attempt to reduce the dose of her regular opioid medication, which she believes makes her foggy-headed and drowsy. She subsequently underwent TPIAT with limited gastric antrectomy on the 30th of January 2020.

A key surgical aspect of the pancreatectomy is to preserve the gastroduodenal & splenic arteries and the splenic vein till the very end of the procedure in order to reduce the warm ischaemia time to the islets[7]. Once resected, the pancreas is cooled down with a preservation fluid and transported to the islet isolation lab. There, the organ is digested enzymatically, followed by gentle mechanical dispersion to free as many islets as possible[7]. Depending on the post-digest tissue volume, the islets can be purified further by means of density gradient centrifugation, although this may not be required given the often fibrotic and atrophic state of the pancreas to start with7. The islet preparation is carried out while the patient remains under general anaesthesia and can take from 3.5 to 6.5 hours[8]. The islet yield is usually expressed as islet equivalents (IEQ) – a unit of islet volume corresponding to an islet size of 150 µm in diameter. The quantity of transplanted islets is an important determinant of the likelihood of insulin independence postoperatively. In literature, a threshold of ⩾2500 IEQ per kg of body weight (IEQ/kg) has been previously shown to correlate with a reasonable metabolic control post-surgery[8]. While the islets are being isolated, a team of experienced hepatobiliary and pancreatic surgeons reconstructs the bile duct drainage and gastric outflow with a jejunal loop anastomosed to both. Isolated islets are subsequently infused through a catheter into the portal vein via a recannulated umbilical vein. Patient XY was transplanted 209,000 IEQ in total into the left portal vein. A bolus of heparin as well as continuous pressure monitoring during the islet infusion allow to reduce the

risk of the patient developing portal vein thrombosis[7].

Post-surgery

There were no intraoperative complications, the patient made a good recovery and was discharged 9 days post-surgery. On discharge, her examination was unremarkable, apart from tenderness around the area where her post-surgical drain used to be inserted; most areas of the surgical wound were dry and intact with some slight serous fluid drainage. The patient was mobilising and comfortable at light levels of exercise.

Administration of insulin immediately after the transplantation is required to maintain the patient normoglycaemic and protect the islet cells from glucose toxicity[1]. The patient was initially given IV insulin and glucose-containing IV infusions to ensure good blood glucose control due to the new onset of diabetes mellitus secondary to TPIAT. When she was able to tolerate oral diet and fluids well, she was switched from IV insulin to fast-acting Novorapid insulin, taken with meals. The patient established good blood glucose control over the course of recovery. On discharge, her prescribed insulin regimen was: long-acting insulin (Levemir) 8 units twice daily as well as the fast-acting form (Novorapid) 2 units with breakfast, 4 units with lunch and dinner. She was also prescribed IM glucagon to inject in the event of severe hypoglycaemia. Lastly, under the supervision of a specialist pain team, the patient will be gradually weaned off the opioid and pain relief medication over the course of 3 months following the surgery.

Pain in chronic pancreatitis

In the 1970s Ammann et al. suggested the "pancreatic burnout hypothesis", which stated that pain in CP should gradually decrease with years as a result of the progressing pancreatic insufficiency[9,10]. However, evidence from a recent retrospective study indicates that this theory applies only to alcoholic CP[11]. Incomplete understanding of the mechanisms initiating and propelling pain in CP translates into a lack of a consensus on the best management strategies. In most CP patients, simple analgesics such as paracetamol or NSAIDs do not provide sufficient pain relief, therefore opioids have become the mainstay of pharmacological pain management. Unfortunately, many patients taking opioids for a prolonged time develop opioid-induced bowel dysfunction with a range of gastrointestinal side effects such as constipation, nausea, vomiting, bloating and dyspepsia[12]. Together, these can paradoxically exacerbate the pain already experienced due to pancreatitis. Moreover, as in XY's case, opioids can have an adverse effect on cognition. Their use also carries a significant risk of developing drug dependence and overdose. This explains why many patients are open to trying out more invasive treatments, despite the risks that come along with surgery.

Pancreatic pain - a "plumbing" problem?

Historically, there have been many proponents of the idea that pain in CP is an outcome of ductal and/or parenchymal hypertension, the so-called "large-duct" form of CP[13]. The causes of such structural abnormalities can be attributed to the gradually progressing fibrosis, presence of pancreatic duct stones and/or strictures or a congenital anatomical variation such as pancreas divisum[14,15]. In such a group of patients, there is a rationale for endoscopic or surgical drainage of the pancreas in order to provide pain relief. This can, for instance, be done by performing a decompressive procedure such as endoscopic stenting or a lateral pancreaticojejunostomy without (the modified Puestow) or with resection of an inflamed pancreatic head (the Frey or Beger procedures)[16]. In the case of patient XY, however, this was not a viable option, since her CT scan revealed a normal looking pancreatic duct. This suggests that patient XY most likely suffers from the rarer, "small-duct" form of CP, characterised by a nondilated main pancreatic duct. The evidence for ductal hypertension leading to mechanical stimulation of the nociceptive pathways and thus being the sole cause of pancreatic pain is scarce. Many studies in CP patients showed that pancreatic duct or parenchymal pressure reduction procedures don't necessarily correlate with a reduction in pain scores[17,18]. Moreover, Bornman et al. observed that the incidence of pancreatic duct obstruction or strictures, as revealed by ERCP, was almost the same in patients with painless and painful forms of CP (69% & 71%, respectively)[19], therefore suggesting that factors other than structural abnormalities of the main pancreatic duct may underlie the aetiology of pain in CP.

Pancreatic pain - a "wiring" problem?

A major reason for our lack of understanding of the pain pathophysiology in CP is the difficulty to model the disease in an animal; one of the best models we currently have is generated by infusing the pancreatic duct of adult rats with trinitrobenzene sulphonic acid, which leads to necroinflammation followed by pancreatic fibrosis[20]. One could argue that an animal model doesn't really reflect the complex pathophysiology of CP in humans. Nonetheless, such studies allowed us to gain some insight into the molecular basis of CP pain pathogenesis. For example, Xu et al. provided electrophysiological evidence for pancreatic sensory neurons undergoing the process of peripheral sensitisation, whereby prolonged stimulation of pancreatic nociceptors by inflammatory molecules released on cell damage (i.e. H+, K+, bradykinin, ATP & prostaglandins) leads to increased excitability & spontaneous firing of the nociceptive fibres[21,22].

Moreover, there seems to be a neuropathic component to the pain in CP as a result of peripheral nerve damage. Histopathological analysis of tissue biopsies from CP patients reveals that pancreatic nerves are frequently invaded by immune cells and the extent of the invasion shows a greater correlation with pain intensity scores than pancreatic fibrosis or disease duration[23]. Electron microscopy confirms substantial damage to the perineurium – the protective sheath surrounding a single bundle of nerve fibres[24]. To make things worse, the phenomenon of neurogenic inflammation is also thought to take place in the pancreas, whereby the nociceptive fibres themselves release key inflammatory molecules, such as Substance P, thus establishing a vicious cycle of self-propelling pain signalling from the pancreas to the brain[22].

These observations, therefore, provide a rationale for invasive procedures that can interrupt the transmission of nociceptive signals from the pancreas. In endoscopic ultrasound-guided celiac plexus blockade, bupivacaine and triamcinolone are injected to block the pain signal transmission, while addition of ethanol can cause complete neurolysis of the fibres[25]. An alternative & more precise procedure is the surgical ablation of splanchnic nerves known as bilateral thoracoscopic

splanchnicectomy (BTS). It is best indicated in patients with small-duct disease and no structural abnormality of the pancreas that could be fixed surgically[26], making patient XY a good candidate for this procedure.

An issue with neuroablative procedures is that long-term outcomes can vary amongst CP patients with many eventually having to rely on analgesia again. Buscher et al. carried out a prospective study evaluating early- and long-term pain relief in 44 patients who underwent BTS[27]. During a median follow-up of 36 months, ~50% of patients experienced pain recurrence and were back on the same or higher daily dose of analgesics. In a subsequent study, they showed that treatment was successful in 52% of patients at 12 months, 38% at 24 months and 28% at 48 months[28]. Although patient XY remained pain-free for 7 years following BTS, she also eventually had to go back to opioid medication. Since studies in pancreatic cancer patients suggest that the effectiveness of repeated neurolysis is low[29], patient XY was directed to be considered for the "last resort" procedure – TPIAT.

Total pancreatectomy with islet autotransplantation – the ultimate solution to pain in CP?

TPIAT was performed for the first time in 1977 by Sutherland et al. at the University of Minnesota[30]. The rationale for excising the whole pancreas is to completely eliminate the putative source of pain, while the simultaneous autotransplantation of islets into the patient's liver allows to ameliorate the severity of the otherwise inevitable diabetes mellitus. Having had taken into consideration the evidence for clinical- as well as cost-effectiveness of the procedure, NHS England decided to routinely commission TPIAT for CP from 2018 onwards. In their policy paper, the Specialised Commissioning Team stated that the procedure is indicated for "intractable pain, which has not responded to nonsurgical treatments, and/or surgical treatments and nerve block interventions where these have either failed or when such treatments are not clinically indicated"[1]. Patient XY suffered from a poorly controlled small-duct form of CP, her islet function was still intact and she hasn't undergone previous surgical procedures of the pancreas, which could reduce her islet yield for the autotransplant, making her a perfect candidate for TPIAT.

TPIAT is still a fairly new and uncommon surgery, with only 4 centres in England equipped to perform the islet isolation on-site[1]. So far, most studies evaluating the effectiveness of TPIAT focused on three key outcomes: pain relief, insulin independence and quality of life (QoL). In 2012 Bramis et al. published a systematic review of five studies evaluating the outcomes of TPIAT in CP patients[31]. Although three studies didn't provide any information on the level of pre-operative morphine use, two studies (Ahmad et al.[32] and Garcea et al.[33]) reported a 116mg and 55mg reduction in daily morphine requirement post-surgery at a 1.5 and 8 years mean follow-up, respectively. In terms of the post-surgery insulin independence, it varied from 46% at a mean follow-up of 5 years to 10% at 8 years. Garcea et al. also assessed the impact of the surgery on patients' life quality – they used a qualitative questionnaire, in which 79% of patients claimed to have experienced a QoL improvement. Another promising line of evidence came in 2014 from a single-centre observational study by Wilson et al., who analysed 5-year follow-up data from 112 post-TPIAT patients[34]. The narcotic independence increased from 55% at 1-year follow-up to 73% at 5-year follow-up. The insulin independence rate decreased between these two time points from 38% to 27%, however, most patients were able to maintain a stable glycaemic control. The outcomes of a single-centre study could, however, be biased by the centre-specific operative techniques and post-operative patient care.

The fact that not all patients achieve a reduction in abdominal pain and daily opioid dose following TPIAT, brings us back to the question of pain pathophysiology in CP. More recent theories suggest that with time, neuroplastic changes at the level of the CNS can lead to central sensitisation. Measurements of contact heat-evoked potentials in CP patients show that stimulation of the upper abdominal area (which shares spinal innervation with the pancreas) is associated with a lack of habituation to repetitive thermal stimuli, pointing towards hyperexcitability of cortical neurons and abnormal pain processing in the brain[35]. MRI studies reveal microstructural changes in cingulate and prefrontal cortices – key brain areas implicated in pain processing and these changes correlate with patients' clinical pain scores[36]. Moreover, Bouwense et al.[37] described a subgroup of CP patients with generalised hyperalgesia, who failed to respond to BTS, further supporting the idea that central sensitisation may play an important role in CP pain pathogenesis. This raises questions about the most optimal timing for a surgical procedure to take place, because once central sensitisation has developed, there is a possibility that the pain becomes independent of the actual peripheral nociceptive inputs from the pancreas, rendering operations such as BTS or TPIAT futile.

Conclusion

Patient XY exemplifies a particularly difficult case of idiopathic CP, in whom neither pharmacological nor neuroablative approaches were able to ensure long-lasting pain relief. Although any sort of pancreatic surgery is known to carry a relatively high risk of post-operative complications and TPIAT can result in a need for life-long insulin replacement therapy, the patient was willing to undergo the procedure, thus showing how unbearable can the pain experienced by CP patients become. Since TPIAT is still a fairly novel procedure, there is a need for large prospective multicentre studies with standardised pain and QoL assessment tools to give us a better idea of the long-term durability of the outcomes in a larger patient population.

With recent advances in our understanding of CP pain mechanisms, it is now becoming clear that CP is not just a disease of the pancreas, but crucially, it's a disorder of pain processing at the level of peripheral and, in some cases, central nervous system. In the future, more accurate "staging" of the progression of pain pathology could allow to predict which patients may realistically benefit from surgical interventions such as BTS or TPIAT. In the meantime, more efforts should be put into developing better pharmacological treatments of CP pain, ideally with fewer side effects than the currently available opioid medication.

Conf icts of interest

None.

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None.

Consent

The patient has consented to the publication of this case study.

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